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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,786	07/25/2006	David Deperthes	KZI-003US	4550

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EXAMINER	
LEE, JAE W	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,786	DEPERTHES ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9,10,12-22,28-34 and 36-46* is/are pending in the application.

4a) Of the above claim(s) *12-16,18-22,37,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6, 9, 10, 17, 28-34, 36, 38-43 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In the preliminary amendment for claims, filed on 03/13/2007, Applicants have canceled claims 1-5, 7, 8, 11, 23-27 and 35, amended claims 9, 39-41 and 43, and newly added claim 46.

Claims 6, 9, 10, 12-22, 28-34 and 36-46 are pending in this application.

Priority

A claim of priority to the PCT/IB04/01040, filed on 04/05/2004 , filed on 07/02/2002, and US Provisional Application 60/460,345, filed on 04/04/2003, is acknowledged.

Election

Applicant's election with traverse of Group I, Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46, alpha 1-antichymotrypsin (ACT), and SEQ ID NO: 19 (Reactive Serpin Loop of MD67), is acknowledged. The traversal is on the ground(s) that restriction of the claims is improper based on the unity of the invention determined during the international stage of the instant application, and furthermore, that the art cited by the Examiner does not teach the general inventive concept of the amended claims.

In response to Applicant's traversal, the Examiner finds arguments not persuasive because the special technical feature, i.e., a "modified" recombinant inhibitor

protein, based on the unity of invention is taught by a prior art reference as shown in the rejection under 35 U.S.C. 102 (see below). Furthermore, the record of International Search Report and the International Preliminary Report on Patentability are "preliminary" and does not dictate the prosecution of US Non-provisional application. As such, regardless of whether those reports cited a prior art or indicate that an invention "might be" patentable, does not prevent or change the restriction requirement set forth during the prosecution of the instant application.

With respect to the restriction/election requirement of a single serpin sequence as listed in claim 9, it is noted by the Examiner that the requirement was not a species election. The restriction requirement for a single serpin sequence is maintained for the reasons explained above.

With respect to the species election between different SEQ ID NOs and (A)-(E), it is noted by the Examiner that they correspond to each other as explained by the Applicant, and that Applicant's election of SEQ ID NO: 19 is (D) MD67. Applicants argue that because the different SEQ ID NOs (as well as (A)-(E)) are share about 99% sequence identity, they represent a single inventive concept. The Examiner finds arguments not persuasive because this is species election and not a restriction requirement, and as such, species election requirement is not based on the unity of invention. As explained in the previous Office Action, they are these distinct structurally and functionally, and the sequences contain multiple mutations at many different locations as shown in Figure 8.

Claims 12-16, 18-22, 37, 44 and 45 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Oath or Declaration

A new oath or declaration is required because of following informalities. The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: the declaration filed on 07/25/2006 and 06/17/2005 does not claim priority to PCT/IB04/01040, filed on 04/05/2004 (see page 3, line 1, where "no such U.S./PCT applications have been filed" is checked).

Claim Objections

Claims 9, 10 and 41 are objected to because of the following informalities:

Claims 9, 10 and 41 are objected to for containing non-elected subject matter.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 28 and 39-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the phrase, "MD 67," which is unclear. It is unclear with respect to what Applicants intend as being encompassed by the phrase.

Claims 28 and 39-43 recite the phrase, "specific for [a or said] kallikrein," and "for said kallikrein," or "specific for kallikrein hK2" and "for said kallikrein hK2," which are unclear. It is unclear with respect to how a recombinant inhibitor protein or an inhibiting fragment thereof is specific for kallikrein. In the interest of advancing prosecution, the phrase is interpreted to be inherent characteristics of a recombinant protein, or an inhibiting fragment thereof, comprising a serpin sequence.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46 are directed to a genus of recombinant inhibitor proteins, or inhibiting fragments thereof, specific for a kallikrein, comprising any serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at any substrate active site sequence resulting in increased binding affinity for said kallikrein.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses an example of a recombinant inhibitor protein, alpha 1-antichymotrypsin (ACT), comprising an amino acid sequence as set forth in SEQ ID

NO: 8. However, this is an inadequate written description for a genus of recombinant inhibitor proteins, or inhibiting fragments thereof, specific for a kallikrein, comprising any serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at any substrate active site sequence resulting in increased binding affinity for said kallikrein.

The specification does not provide a disclosure of any particular structure to function/activity relationship in any recombinant inhibitor protein or any inhibiting fragment thereof, comprising any serpin sequence comprising any RSL, wherein the modified RSL is modified by any substrate active site sequence. The specification also lacks description with respect to what function, if any, is required for any recombinant inhibitor protein or any inhibiting fragment thereof, comprising any serpin sequence comprising any RSL, wherein the modified RSL is modified by any substrate active site sequence. Further, the specification fails to describe any identification of structural characteristics or properties of any recombinant inhibitor protein or any inhibiting fragment thereof, comprising any serpin sequence comprising any RSL, wherein the modified RSL is modified by any substrate active site sequence. Given the lack of additional representatives of a genus of recombinant inhibitor proteins or inhibiting fragments thereof, comprising any serpin sequence comprising any RSL, wherein the modified RSL is modified by any substrate active site sequence as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a recombinant inhibitor protein, alpha 1-antichymotrypsin (ACT), comprising an amino acid sequence as set forth in SEQ ID NO: 8, does not reasonably provide enablement for any recombinant inhibitor protein, or any inhibiting fragment thereof, specific for a kallikrein, comprising any serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at any substrate active site sequence resulting in increased binding affinity for said kallikrein. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46 are so broad as to encompass any recombinant inhibitor protein, or any inhibiting fragment thereof, specific for a kallikrein, comprising any serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at any substrate active site sequence resulting in increased binding affinity for said kallikrein.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the "recombinant inhibitor protein," "inhibiting fragment thereof," "serpin sequence," "modified Reactive Serpin Loop," and "substrate active site sequence." Since the amino acid sequence of a peptide determines its structural and functional properties, predictability of which peptides can be used while obtaining the desired function requires a knowledge of and guidance with regard to which amino acids in the peptide's sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the peptide's structure

relates to its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different peptides/proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any recombinant inhibitor protein because the specification does not establish: (A) regions of the protein structure which may be modified without affecting its desired biological activity, i.e., serine protease inhibiting activity; (B) the general tolerance of any recombinant inhibitor protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any recombinant inhibitor protein with an expectation of obtaining the desired biological function; (D) adequate guidance with respect to how all modifications of any substrate active site sequence affect the structure and function of any RSL, therefore, any recombinant inhibitor or any inhibiting

fragment thereof, and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to make and use any recombinant inhibitor protein, or any inhibiting fragment thereof, specific for a kallikrein, comprising any serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at any substrate active site sequence resulting in increased binding affinity for said kallikrein.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any recombinant inhibitor protein, or any inhibiting fragment thereof, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43 and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Schechter et al. (Reaction of Human Chymase with Reactive Site Variants of alpha 1-Antichymotrypsin, Journal of Biological Chemistry, 1993, 268(31): 23626-23633) in view of an evidentiary reference, Rubin et al. (Cloning, Expression, Purification and Biological Activity of Recombinant Native and Variant Human alpha1-Antichymotrypsins, Journal of Biological Chemistry, 1990, 265(2): 1199-1207).

The instant claims are drawn to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at least one substrate active site sequence resulting in increased binding affinity for said kallikrein.

Schechter et al. teach the reaction of Human Chymase with reactive site variants of alpha 1-Antichymotrypsin (ACT). Schechter et al. specifically teach a recombinant inhibitor protein, comprising a serpin sequence, i.e., ACT, comprising a modified reactive serpin loop, i.e., recombinant ACT variants or rACT comprising reactive loop (shown in Table 1 on pg. 23629, and under "rACT variants" on pg. 23627), including rACT P3-P'3cas variant, wherein the modified RLS is modified by at least one substrate active site sequence resulting in increased binding affinity to a serine proteinase,

Chymase (see pg. Figures 1, 2 and 3, and 112 2nd paragraph rejection above), thereby anticipating claims 9, 17, 38, 39, 40, 42, 43 and 46.

The evidentiary reference of Rubin et al., which is cited in the reference of Schechter et al. ("rACT variants" on pg. 23627), teaches cloning, expression, purification and biological activity of recombinant native and variant human alpha 1-Antichymotrypsins. Rubin et al. specifically teach a method of producing recombinant variants of ACT, comprising (A) selecting a polynucleotide sequence encoding a substrate active site, i.e., selecting DNA sequence for site-directed mutagenesis (see Figure 3 on pg. 1201, and under section heading "Site-directed Mutagenesis" on pg. 1200), (B) introducing said sequence into a sequence encoding a serpin, i.e., ACT, (C) expressing said native or variant rACT proteins in E. coli, culturing overnight at 30 degrees Celsius, and (D) extracting said recombinant protein from E. coli cell lysate using centrifugation and sonication, and purifying said proteins using affinity chromatography, i.e., Sepharose Fast Q, and DNA-cellulose columns (see under section heading "Purification and Characterization of Recombinant Antichymotrypsins" on pg. 1201-2), thereby anticipating claims 28, 30, 32, 33 and 36. Therefore, Schechter et al. anticipates the Applicants' claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43 and 46 drawn to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified b at least one substrate active site sequence resulting in increased binding affinity for said kallikrein.

Conclusion

Claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER